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REVIEW

NEUROENDOCRINE ACTIVATION AS A TARGET OF MODERN CHRONIC HEART FAILURE PHARMACOTHERAPY

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Abstract: At present, a constant progress in pathophysiology understanding and treatment of the chronic heart failure (CHF) is arising. The current CHF pharmacotherapy is complex, involving factors affecting the renin-angiotensin-aldosterone system (RAAS), β-blockers, diuretics and vasodilatators. There are also significant efforts to introduce in CHF pharmacology novel therapeutic strategies, based on the other neurohormonal mechanisms activated in CHF. They include vasopressin receptor antagonists (VRA; vaptans), endothelin receptor antagonists (ERA; sentans), agents relating to the natriuretic peptides system (neutral endopeptidase inhibitors; NEPI and vasopeptidase inhibitors; VPI) and anticytokines agents (anti TNF-α immunoglobulin or TNF-α scavenger receptor; Etanercept). In this article we briefly describe the modern approach to CHF systemic treatment.

Keywords: chronic heart failure pharmacotherapy, vasopressin receptor antagonists (VRA), endothelin receptor antagonists (ERA), vasopeptidase inhibitors (VPI), anticytokine therapy

Abbreviations: ACE – angiotensin converting enzyme, ACEI – angiotensin converting enzyme inhibitors, ADH – antidiuretic hormone, ANP – atrial natriuretic peptide, ARB – angiotensin receptor blockers, AVP – arginine vasopressin, BNP – brain natriuretic peptide, CHF – chronic heart failure, ERA – endothelin receptor antagonists, ET-1 – endothelin, NEPI – neutral endopeptidase inhibitors, RAAS – renin angiotensin aldosterone system, SIADH – syndrome of inappropriate antidiuretic hormone secretion, SNS – sympathetic nervous system, TNF – tumor necrosis factor, VPI – vasopeptidase inhibitors, VRA – vasopressin receptor antagonists, VSMC – vascular smooth muscle cells

Pathophysiology and symptomatology of chronic heart failure

Chronic heart failure (CHF) is a condition characterized by heart insufficiency in adequate blood supplying, delivering to peripheral tissues. The main hemodynamic pathomechanism of CHF is associated with progressive decrease of the cardiac output, arising from impairment heart function as a pump in cardiovascular system (systolic heart failure). Diastolic ventricular dysfunction results in intravascular and interstitial volume overload, which also leads to lower cardiac end diastolic volume and, in consequence, lower cardiac output – to poor tissue perfusion. Clinically, taking into consideration the course of the disease and predominance symptoms, heart failure is divided into acute and chronic one and into right ventricle, left one or both ventricles cardiac insufficiency. The CHF incidence increases with age. About 1% of patients older than 50 years experience heart failure, but in people aging at least 80, 10% of CHF prevalence is observed with the 40% of isolated systolic and both 30% of diastolic and 30% of mixed chronic heart failure occurrence (1–3).

The CHF symptomatology is complex, focused on both peripheral and pulmonary venous congestion and decreased effective arterial blood volume (EABV) – tissue perfusion. Thus, main CHF symptoms arise from venous blood accumulation before heart: peripheral and pulmonary interstitial edemas (secondary to volume overload), dyspnea and non-productive cough (caused by pulmonary congestion), orthopnea (resulting from blood redistribution from the legs to the central circulation when patient lies down at night), jugular veins enlargement and hepatosplenomegaly. The symptoms originated from decreased cardiac output are also observed: fatigue (associated with reduced blood oxygenation), intolerance of physical activity (inability to increase cardiac output), restlessness and confusion. Chronic heart failure is a common end way of all

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heart diseases. It can be a result of both volume (e.g., in aortic or pulmonary valve insufficiencies, congestive cardiomiopathy, congenital heart disease) or pressure overload (in hypertension, aortic or pulmonary valve stenosis, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease), restricted filling of the heart (mitral or tricuspid valve stenosis, constrictive pericarditis) or decreased cardiomyocyte contractility (coronary artery disease, connective tissue disease, poisons and drugs: alcohol, cobalt, antineoplastic drugs, especially antracyclines) (1–3).

Heart dysfunction caused by any factors mentioned above, results in its progressive worsening which triggers compensatory mechanisms activation. Initially, both the sympathetic and renin-angiotensin-aldosterone system (RAAS) activity provides background to restore cardiac output and peripheral perfusion of vital organs. However, long-term sympathetic stimulation, together with RAAS activation lead to increased preload (due to venous vasoconstriction, increased venous return, augmented by water and sodium renal retention) and afterload (due to increased arterial peripheral resistance), which aggravate heart insufficiency symptoms. Moreover, two powerful vasoconstrictory peptides are secreted – vasopressin (AVP) from posterior pituitary gland and endothelin (ET) from endothelial cells. These peptides, together with aldosterone, are co-responsible for cardiac remodelling and deposition of collagen in the interstitial matrix. Additionally, AVP augments renal reabsorption of water. In CHF, natriuretic peptides system is also engaged to counteract initially the cardio- and vasopressive effects mentioned above. However, this compensatory mechanism is not effective to prevent from further progress of the chronic heart disease. CHF is also associated with cytokines secretion, released from various immunoreactive cells in response to injury. In CHF patients, TNF-α and Il-1 plasma levels are increased. They appear to play an important role in myocyte hypertrophy and apoptosis (3, 4).

Summing up, neuroendocrine activation plays a key role in CHF pathogenesis and it seems to be attractive target of pharmacological interventions. The purpose of this mini review is to shortly describe current and possible therapeutic perspectives, based on the influence into neuroendocrine, compensatory mechanisms, activated in CHF. They are summarized in Table 1.

The renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system

Currently administrated drugs, effective in CHF treatment, may be distinguished in RAAS inhibition, β-blockers, diuretics or agents which diminish vascular resistance (such as hydralazine and nitrates, dihydropyridine and nondihydropyridine calcium channels blockers).

The renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) play important role in pathogenesis of CHF, being the most important compensatory mechanisms, triggering in CHF development. Physiologically, RAAS and SNS are responsible for cardiac and vasomotor activity (causing an increase in total peripheral resistance and mean blood pressure), renal intracapillary pressure, glomerular filtration rate, maintain optimal salt and water homeostasis and control of tissue growth. These systems are greatly activated in CHF in response to threats that compromise blood pressure stability and extracellular fluid volume homeostasis, such as decrease of effective artery blood volume (in CHF) and in many other unstable hemodynamic conditions (5, 6).

The key element of RAAS system – angiotensin II (AII) mediates its effects by two kinds of receptors – AT1 and AT2. AT1 receptors are distributed in the blood vessels, kidney, heart, liver and brain whereas AT2 ones – in the adrenal medulla, uterus, ovary, blood vessels and certain brain regions. Activation of AT1 leads to the systemic and renal vasoconstriction, increased renal sodium reabsorption, vascular smooth muscle growth, oxidative stress and inflammatory cytokines activation, endothelial dysfunction and increased plasminogen activator inhibitor 1 activity. On the contrary, biological effects mediated *via* AT2 stimulation include: systemic and renal vasodilatation, decreased renal sodium reabsorption, decreased inflammation and myocyte hypertrophy with cardiac muscles fibrosis. Moreover, activation of AT1 receptors in zona glomerulosa of the supraadrenal glands stimulates the aldosterone secretion. Aldosterone is a mineralocorticoid, which acts *via* receptors expressed in the kidneys and results in sodium and water retention (thus, it plays an essential role in blood pressure and volume regulation). It is not only under control of AII, but its secretion is also mediated by other factors, such as hyponatremia, hyperkalemia and hypovolemia. Moreover, recently it has been shown that aldosterone receptors are found in other tissues including heart, brain and blood vessels and contribute to their fibrosis and remodelling (together with angiotensin) (5, 6).

Overexpression of RAAS together with increased SNS activity observed in CHF contribute to further CHF development, hypertension and related target-organ damage. The impact of RAAS on

Table 1. Neuroendocrine systems activated in chronic hart failure (3, 4)

	Biochemical properties	**Postsynaptic receptors – place of action**	**Effects cardiovascular system and others**	**Preload**	**Afterload**	**Pharmacological intervention**	**Safety and survival improvement**
Sympathetic nervous system	Noradrenaline (catecholamine)	α_1, β_1, β_2	Heart: inotropism ↑ chronotropism ↑ dromotropism ↑ Myocyte hypertrophy Vasoconstriction Renin secretion		↑	β-blockers	yes
Renin-angiotensin-aldosterone system	Renin (enzyme) Angiotensin II (octapeptide) Aldosterone (steroid)	AT_1, AT_2 Aldosterone receptors	Heart inotropism ↑ Myocardial hypertrophy Myocardial fibrosis Vasoconstriction Sodium retention	↑	↑	Angiotensin converting enzyme inhibitors (ACEI) Angiotensin II receptor blockers (ARB) Aldosterone antagonists	yes yes yes
Vasopressin	Nine aminoacids peptide	V_1, V_2 Water retention	Vasoconstriction	↑	↑	Vasopressin receptor antagonists (VRA)	unsettled
Endothelin-1	Peptide (21AA)	ETA_A, ETB_B	Vasoconstriction Myocyte hypertrophy		↑	Endothelin receptor antagonists (ERA)	unsettled
ANP\BNP	ANP–peptide (28AA) BNP-peptide (32AA)	NPR_A, NPR_B, NPR_C	Vasodilatation Natriuresis Myocyte antihypertrophy	↓	↓	Neutral endopeptidase inhibitors (NEPI) Vasopeptidase inhibitors (VPI)	unsettled unsettled
TNF-α	Polypeptide (17kDa)	TNFR-1,2	Heart: inotropism ↓, left ventricle dilatation and dysfunction			antiTNF-α-IgG TNF-α soluble receptor (Etanercept)	unsettled unsettled

kidneys manifests by its effects on intravascular volume and blood pressure regulation. The raise of blood pressure after both RAAS and sympathetic stimulation results in direct vasoconstriction of the systemic vessels. Upon activation of AT1 receptors of the efferent arteriole and its contraction, AII reduces the renal blood flow and increases the glomerulal filtration and proximal sodium and fluid reabsorption. Additionally, aldosterone has its major effect in distal nephron sodium reabsorption through the epithelial sodium channel. The renal AT1 receptor activation promotes collagen deposition (through reduction in protein degradation by inhibition of proteases), inflammatory process by production of the inflammatory factors (TGF-β, PDGF, and nuclear factor κB synthesis) and fibroblasts activation. These effects lead to enhanced progressive renal injury from glomerulosclerosis and tubulointerstitial fibrosis. The similar consequences of activated RAAS are observed in heart, including: myocyte hypertrophy with left ventricular hypertrophy, fibrosis, increased expression of matrix metalloproteinase and augmented oxidative stress. These disturbances predispose to heart failure through the diminished contractility and/or abnormal diastolic filling as well as cardiac rhythm perturbations. Moreover, RAAS is responsible for vasoconstrictive, hypertrophic, atherosclerotic, inflammatory and prothrombotic effects in coronary arteries. The systemic blood pressure elevates through total peripheral resistance increase, vascular smooth muscles remodelling and endocrine and metabolic endothelial disturbances (especially depletion in endothelial nitric oxide secretion, sympathetic activity enhancement and augmented response to vasoconstrictor substances) (7–9).

Thus, suppressing RAAS and SNS are the most important pharmacological targets in treatment of the CHF. Agents acting *via* this mechanism are regarded to be of essential meaning in present CHF pharmacotherapy. The guidelines recommend selective β_1 antagonists administration (in appropriate doses; adequate to prevent from late organ damage but not exacerbating the heart insufficiency) (10, 11). Currently used RAAS inhibitory drugs include: angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and aldosterone antagonists (spironolactone, eplerenone) (12). Moreover, now there is an additional possibility of RAAS inhibition, using renin inhibitors ("skirens", e.g., aliskiren) and a new class of combined ACE and neutral endopeptidase (NEP) inhibitors – vasopeptidase inhibitors (VPI) (see below).

Summing up, general agreement exists that RAAS and SNS inhibition in heart failure provides beneficial effects: normalization of elevated blood pressure, regression of ventricular hypertrophy, inhibition of vascular smooth muscle growth, stabilization of renal function and improvement in proteinuria (especially in diabetic patients), reduction in activation of sympathetic nervous system, normalization of endothelial behavior and enhancement of fibrinolytic activity (13–17). Agents inhibiting RAAS and SNS activity are regarded to be the most important pharmacological intervention in CHF pharmacotherapy. The further part of this mini-review will be focused on the other new neuroendocrine changes, which also seem to be interesting pharmacological targets.

Vasopressin. Vasopressin receptor antagonists (VRA) – vaptans

The next essential factor playing role in CHF pathophysiology is vasopressin (AVP) – antidiuretic hormone (ADH), which is produced by neurosecretory hypothalamic periventricular and supraoptic nuclei. AVP is then released from posterior pituitary in response to hyperosmolality and hypovolemia. It is responsible for augmented water reabsorption in distal renal tubules and for blood vessel contraction. These effects are mediated by AVP interacting with membrane receptors V1, V2, located in distal organs (18, 19).

The AVP increase is observed in CHF, being a result of effective arterial blood volume decrease, diminished renal blood flow and baroreceptors stimulation, which result in compensatory vasopressin secretion (and other neuroendocrine activation, including RAAS and SNS). Hyponatremia extends as a result of disturbed sodium balance, secondary to hyperaldosteronism development and vasopressin overproduction. These hormones favor CHF progression, causing an increase in total peripheral resistance and contributing to adverse heart remodelling in long-term survival perspective (20).

Thus, pharmacological concept of VRA, the so-called "vaptans" or "aquaretics" administration in CHF treatment has been introduced. Taking into consideration pathophysiological implications, there are possibilities of selective or non-selective vasopressin receptors antagonism. However, the beneficial hemodynamic effects observed after selective V1A receptor antagonists (vasodilatation, antiplatelet) are partly abolished by an increase of water reabsorption arising from coexistence of renal V2 receptor stimulation. Thus, there is no background to administrate selective V1A VRA in CHF.

Table 2. Selected new agents studied in CHF (and other cardiovascular entities) treatment (23, 31, 44)

International name INN Name	Trade name (if was given)	Pharmacological action; Receptor selectivity	Confirmed or suggested according to clinical studies indication for use
VASOPRESSIN RECEPTOR ANTAGONISTS (VRA)			
Tolvaptan	——-	V2 antagonist	Hypervolemic hyponatremia in CHF Polycystic kidney disease (PKD)
Lixivaptan	——-	V2 antagonist	Hypervolemic hyponatremia in CHF Euvolemic hyponatremia in SIADH
Satavaptan	AQUILDA	V2 antagonist	Euvolemic hyponatremia in CHF Ascites in liver cirrhosis
Mozavaptan	PHYSULINE	weak V1A antagonist strong V2 antagonist	Euvolemic hyponatremia in SIADH
Conivaptan	VAPRISOL	weak V1A antagonist strong V2 antagonist	Hypervolemic hyponatremia in CHF Euvolemic hyponatremia in SIADH
Relcovaptan	——-	V1A antagonist	Preterm labour Dysmenorrhoea Reynolds disease
NATRIURETIC PEPTIDES NEUTRAL ENDOPEPTIDASE INHIBITORS (NEPI) VASOPEPTIDASE INHIBITORS (VPI)			
recombinant BNP	NESIRITIDE NATRECOR	NPR-A agonist	CHF, Coronary artery disease, Pulmonary hypertension
Sampatrilat	——	NEP inhibition ACE inhibition	CHF Hypertension
Gemopatrilat	——		
Fasidotril	——		
Omapatrilat	VANLEV		
ENDOTHELIN RECEPTOR ANTAGONISTS (ERA)			
Ambrisentan	LETAIRIS (USA) VOLIBRIS (EU)	ETA/ETB dual antagonist	Pulmonary hypertension
Atrasentan	XINLAY (USA) ETA	antagonist	Prostate cancer
Bosentan	TRACLEER (EU)	ETA/ETB dual antagonist	CHF, Pulmonary hypertension
Clazosentan	PIVLAZ	ETA antagonist	Subarachnoid hemorrhagia
Darusentan	—-	ETA antagonist	Coronary artery disease Hypertension
Tezosentan	VELETRI	ETA/ETB dual antagonist	Acute Heart Failure Pulmonary hypertension
Sitaxsentan	THELIN (EU)	ETA antagonist	CHF Pulmonary hypertension
TNF-α ANTAGONISTS			
Recombinant human TNF-α receptor	ETANERCEPT	TNF-α	CHF
Anti TNF-α monoclonal antibody	INFLIXIMAB	TNF-α	CHF

Similarly, it might be expected that selective antagonism of renal V2 receptor, causing the aquaretic effect is accompanied by V1 unoccupied receptors activation, leading to an increase of vascular resistance. The rational conclusion of limitations mentioned above is a usage of double V1A/V2 antagonists. On the other hand, studies focused on selective V2 vaptans in CHF treatment have not revealed exacerbation of this clinical entity so far. It seems possible, that pressive responses resulting from unoccupied V1A receptors stimulation are not strong enough to outnumber the antagonistic effect of VRA on renal V2 receptors.

It is believed that VRA, causing an abolition of water reabsorption in distal renal tubules and inducing increased urine excretion (aquaretic effect) lead to hemodynamic improvement in CHF, which is secondary to preload decrease. Thus, in clinical practice, selective V2 receptor antagonists (aquaretic effect) and non-selective V1A/V2 ones (aquaresis with peripheral vasodilatation) have essential pathophysiological meaning (18, 19, 21–23). The examples of selected VRA are given in Table 2.

Natriuretic peptides. Neutral endopeptidase and vasopeptidase inhibitors

The next important element of compensatory response, developing in chronic CHF, includes an increase in natriuretic peptides levels. The family of these compounds is composed of: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-natriuretic peptide (CNP). Both ANP and BNP are synthesized mainly in response to increased left ventricle end diastolic pressure and intra-arterial pressure loads. The other factors involved in ANP/BNP release are: endothelin, angiotensin II and cytokines such as: TGF-β, Il-1, LPS, FGF (24–26).

Natriuretic peptides modulate cardiovascular functions *via* natriuretic peptide receptor (NPR)-A and NPR-B, causing systemic vasodilatation, RAAS and sympathetic nervous system inhibition. They also cause afferent glomerular arterioles dilatation together with efferent ones contraction, leading to diuresis enlargement. ANP/BNP also diminish sodium reabsorption in renal tubules causing natriuresis. Additionally, they increase vascular permeability and intravascular fluid shift into extravascular space, which augment hypotensive effect caused by vasodilatation and natriuresis. ANP/BNP also diminishes vascular smooth muscles proliferation and cardiomyocytes remodelling (24).

Natriuretic peptides released in CHF are responsible for beneficial compensatory effects, contributing to decrease of both preload and afterload. Many studies revealed proportional relationship between increased natriuretic peptides level and intensification of both systolic and diastolic CHF symptoms. At present, ANP/BNP measurement becomes a valuable diagnostic tool, especially in case of oligosymptomatic patients in early CHF stage. Assay of natriuretic peptides level also creates possibility of estimation of CHF pharmacotherapy efficacy (effective treatment results in a decrease of plasma natriuretic peptides level) (25–28).

The predominant directions in searching for agents influencing natriuretic peptides system are inhibitors of ANP/BNP enzymatic breakdown. Two classes of them are distinguished: neutral endopeptidase inhibitors (NEPI) and vasopeptidases inhibitors (VPI) – enzymes responsible for various biological peptides degradation, including ANP and BNP (24, 26). Neutral endopeptidase (neprilysin) is an enzyme found especially in renal tubules and nephrons. In several clinical studies, administration of candoxartil – one of NEPI, increased natiuresis and diuresis. Despite these effects, suggesting the ANP increase after candoxartil, no significant reduction of blood pressure was noted, both in hypertensive and normotensive participants. The reason of the limited hypotensive efficacy of NEP inhibitors may be associated with small enzymatic selectivity of these agents. Beside ANP/BNP, NEP is an additional pathway of many other peptides degradation, including vasopressive ones such as angiotensin or endothelin. NEP blockade accomplished by candoxartil and analogues leads to simultaneous plasma level increase of both natriuretic peptides and vasoconstrictory factors as well. These changes cause an opposite impact on blood pressure regulatory mechanisms, without finally expected hypotensive effect. Despite a lack of the afterload decrease, NEP inhibitors are reported to be beneficial in CHF treatment, especially because of lowering the preload, secondary to natriuresis with no direct impact on RAAS and sympathetic activity. Hypothetically, in a close future, NEP inhibitors may be considered as an alternative for "classical" diuretics, commonly administrated in CHF patients (24, 26, 29).

A lack of NEP selectivity and pharmacological contrary effects after NEP inhibitors (simultaneous increase cardio- and vasopressive peptides together with natriuretic peptides) brought up interest on agents blocking of two enzymes – neutral endopeptidase and angiotensin converting enzyme (ACE). New, unique compounds were discovered called vasopeptidase inhibitors – VPI. They combine dou-

ble activity – simultaneous NEP inhibition (as classic NEP inhibitors) with ACE blockade (as ACE inhibitors).

According to VPI pharmacodynamic properties, combination of dual enzymatic blockade leads to an increase of natriuretic peptides with no accompanying increase of angiotensin II and aldosterone. Moreover, an elevation of kinin level is indirectly observed, also secondary effect of ACE inhibition. It is regarded that beneficial hemodynamic effects elicited by VPI result not only from direct impact on ANP/BNP and RAAS, but also from kinins overactivity. Bradykinin is broken down by both NEP and ACE, thus VPI administration causes considerable augmentation of kinins action. It is associated with subsequent nitric oxide (endothelial derived relaxing factor) and prostacyclin increase. Thus, it seems that VPI also show antiplatelet effects and improve dysfunction of the blood rheology. It was also found that VPI caused adrenomedullin increase, however, it is not explained if this peptide has significant role in VPI renal action (26, 29–31).

The important limitations of VPI introduction into general practice are their possible side effects. VPI administration was associated with various adverse effects: dizziness, headache, nausea. Dry cough was also a significant VPI adverse effect, similarly to ACE inhibitors. However, the most important unpleasant side effect was angioedema. This phenomenon is also observed in 0.1–0.5% patients receiving ACE inhibitors. The daily administrated omapatrilat (in a dose of 20 mg), generated angioedema about three times more often than ACE. It is not known, if other VPI cause this harmful effect with such frequency (32). The examples of currently studied NEPI and VPI are presented in Table 2.

Endothelin. Endothelin receptor antagonists (ERA)

Endothelin-1 (ET-1) is a 21-amino acids peptide which is found to possess 10-times stronger vasoconstrictory and pressive properties than angiotensin II. ET-1 is secreted under the influence of various growth factors and cytokines, such as: thrombin, TGF-β, TNF-α, insulin, free oxygen radicals, catecholamines, angiotensin II, vasopressin and hypoxia, and as a response to increased mechanical stimuli, such as shear stress. ET-1 synthesis is inhibited by nitric oxide, natriuretic peptides, heparin and prostaglandins. The main sources of ET-1 are vascular endothelium, cardiomyocytes, vascular smooth muscles, renal tubules, nephron mesangium, pituitary gland, liver and lungs, which implicates that this peptide plays important regulatory functions in various organs (33, 34).

Endothelin acts *via* membrane receptors, labelled as ETA and ETB. ETA receptor is located mostly on vascular smooth muscle cells (VSMC), whereas ETB on both VSMC and endothelium. Initially it was suspected that ETA VSMC receptor stimulation causes vasoconstriction while endothelial ETB – vasodilatation. At present, it was proved that both ETA and ETB receptors are situated on VSMC and they induce coronary, renal, portal and intestinal vasoconstriction. Thus, finally strong contracting and proliferative ET-1 effect is a result of ETA/ETB VSMC receptors activation, only partly abolished by the influence of ET-1 on endothelial ETB receptor and, as a consequence, a release of endothelial derived relaxing factor (EDRF) together with prostacyclin (PGI_2) and nitric oxide (NO) (33–35).

In CHF, an increase of ET-1 occurs, which correlates with severity and advancement of CHF. Initially, ET-1 greatly increases the contractility of cardiac muscle and contributes to the maintenance of vascular tone, thus acting with other neuroendocrine mechanisms as early compensatory response. Moreover, ET-1, causing renal blood flow decrease, leads to glomerular filtration rate depletion and to sodium retention. However, in long-term perspective, ET-1 causes cardiac remodelling, contributing to cardiac contractility impairment and to CHF acceleration. Apart from cardiac and vascular effects, ET-1 is closely associated with RAAS. ET-1 activates angiotensin converting enzyme, thus leading to angiotensin II synthesis. On the other hand, angiotensin II also causes increased endothelin secretion. The synergistic action of angiotensin II, aldosterone, endothelin and vasopressin results in pathological cardiac remodelling, progressive impairment of cardiac contractility and increase of afterload, conditioned by vascular resistance elevation. Additionally, angiotensin II and endothelin are proved to have proarrhythmic features, which also favor further CHF progression. Taking into consideration the mechanisms mentioned above, it should be expected that ET-1 blockade (similarly to RAAS inhibition) in CHF might be associated with beneficial hemodynamic changes, protecting from further heart failure exacerbation. There are attempts of introduction in modern CHF pharmacotherapy new agents acting through ET-1 blockade – endothelin antagonists – ERAs (34, 36, 37).

Currently investigated ERAs are selective ETA single receptor or dual ETA/ETB blockers. Considering some opposite effects originated from

different receptor activation indicated above, one should expected partly opposite pharmacological results, depending on ERA selectivity. In accordance with expectations, antagonistic impact on ETA receptor leads to vasodilatation while selective ETB blockade also results in vasodilatation and has antiproliferative effect, but with some harmful (endothelial EDRF, PGI_2, NO decrease) influence. Thus, some preclinical and clinical studies implicate that selective ETB blockade may impair systemic hemodynamic feature and there is no indications for their introduction to CHF treatment. At present, the common belief of superiority and rationale of dual ETA/ETB or selective ETA endothelin receptor antagonists' administration exists (35).

The adverse effects occurred during ERAs treatment include headache, nausea, rhinitis, sinusitis, dyspnea, chest pain and dose-related anemia. Most of them are the result of non-specific, vasodilatatory ERAs feature. These agents also exert hepatotoxicity, probably because of their cholestatic effect. ERAs also cause essential pharmacokinetic interactions, effecting Cyp450 activity, which metabolize many drugs (34). Preclinical studies confirmed that these agents are teratogenic, thus they are contraindicated in pregnancy. In animal models, persistent ductus arteriosus and craniofacial malformations were observed. The selected ERAs agents, studied as a potentially useful in CHF treatment, are presented in Table 2.

Cytokines. Anticytokine therapy

Apart from essential role of neurohormones in the CHF development, current studies are also focused on the proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α). This molecule is produced as a prohormone, containing 233 aminoacids and then processed into a 157-amino acids native form. The TNF-α synthesis is increased in response to various stimuli: lipopolisaccharide, viruses, fungal or parasitic agents, and interleukin-1. On the other hand, TNF-α regulates the expression of many various cytokines: interleukin-6, platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β), platelet activating factor (PAF) and other eicosanoids. Once released from cells, TNF-α interacts with its receptors: a high affinity TNFR-1 receptor and low affinity TNFR-2 one, which differ each other with the signalling pathways. TNF-α exerts pleiotropic effects – it is coresponsible for paracrine and autocrine regulation of leukocytes and endothelial cells. It enhances chemotaxis, phagocytic and cytotoxic activity of immunoreactive cells, promotes leucostasis by inducing increased expression of intracellular adhesion molecules (ICAMS) and endothelial leukocyte adhesion molecules (ELAMS) at sides of inflammation. Thus TNF-α is a key factor of inflammatory process.

At higher concentrations, TNF-α exerts endocrine effects, causing metabolic wasting, microvascular coagulation, hypotension, heart contractility impairment and fever. This cytokine also modulates both tissue destruction and rebuilding by activating of fibroblasts and mesynchymal cell proliferation. It is also cytotoxic to endothelial cells and induces the biosynthesis of collagenases, proteases, reactive oxygen species and arachidonic acid metabolites. TNF-α plays an important role in cardiac remodelling and favors heart failure exacerbation. Physiologically, high level of circulatory TNF-α causes the TNFR extracellular protein liberation into the circulation. The soluble receptors are able to bind ligand and thus to inhibit the adverse effects of high TNF-α level, thus serving as a clearance receptor that can neutralize the activities of this cytokine. In high amount TNF-α level, this clearance mechanism is inefficient (38).

It was also discovered, that TNF-α also participates in CHF pathogenesis. The level of this cytokine is elevated, especially in patients with end stage of heart failure and cachexia, potentiating the negative inotropic effect. It seems that TNF-α effectively uncouples the β-adrenergic receptors from adenylyl cyclase, activates metalloproteinases and inhibits the expression of inhibitors of metalloproteinases, leading to extracellular matrix remodelling. TNF-α also provokes a hypertrophic growth response in cardiac myocytes, which may be a response to hemodynamic stress (38–42).

Based on the findings, the concept of anticytokine pharmacological TNF-α blockade in CHF raised. It was observed that β-adrenergic agonists may inhibit TNF-α production, probably by elevating intracellular cAMP level. Phospodiesterase inhibitors also can diminish TNF-α secretion. Pentoxyfilline demonstrated beneficial effect in failed heart which was associated with decreasing TNF-α level. It was also found that adenosine is a potent TNF-α blocker. The next therapeutical strategy is based on the passive immunization mechanisms. Monoclonal antibodies against TNF-α (e.g., Infliximab) were effective in ameliorating the effects of sepsis, cancer and inflammatory bowel diseases. There is a question if administration of anty-TNF-α Ig in CHF also results in therapeutic efficiency. The next therapeutic option of myocardial TNF-α suppression is the use of recombinant TNF-α soluble

receptor (Etanercept). This agent has already been approved by FDA in rheumatoid arthritis treatment. The clinical trials estimating rationale for Etanercept using in CHF are still ongoing, however, the preliminary results suggest that this agent is well-tolerated and causes decreasing of circulatory TNF-α of about 70% for at least 14 days, results in clinical CHF course and quality of life improvement (38, 43).

Conclusions

Over the past decades, the approach to CHF treatment has completely changed. In the past, CHF was regarded to be a clinical entity characterized mainly by poor contracting heart. Nowadays, CHF is understood as a complex autonomic – neuroendocrine disorder. Thus, the previous pharmacological guidelines based on inotropic agents, diuretics and vasodilatators have been re-evaluated. Lately investigators interest is focused on CHF neurohormonal mechanisms (VRA, ERA, NEPI, VPI, anti-TNF-α). However, results of clinical trials are still limited and scrappy. Further studies are required to confirm additional areas of modern CHF treatment. Introduction of new classes of medicaments, related to autonomic and neuroendocrine pathomechanisms, seems possible.

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